acetonitrile with various *t*-aminoethyl chlorides, using sodium amide or lithium amide as described.[13-16]

Method B.—The basic amides were prepared by 90% sulfuric acid hydrolysis of the nitriles obtained by method A.[14,16]

Method C.—A mixture of 0.17 mole of the amidone-type amide and 1 mole of thionyl chloride was prepared in an ice-bath. No reaction occurred. This mixture was heated on a steam-bath for one to three hours, made strongly alkaline with sodium hydroxide and extracted with ether. The extracts were dried over potassium carbonate, and the ether removed by evaporation. The residual basic materials were purified by crystallization or fractionation *in vacuo* followed by salt formation as indicated in the table.

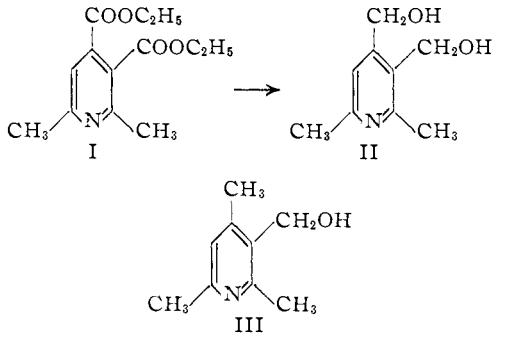
RESEARCH DEPARTMENT
PHARMACEUTICAL LABORATORIES EUPHARMA
TURNHOUT, BELGIUM

Lithium Aluminum Hydride Reduction of Diethyl 2,6-Dimethyl-3,4-pyridinedicarboxylate

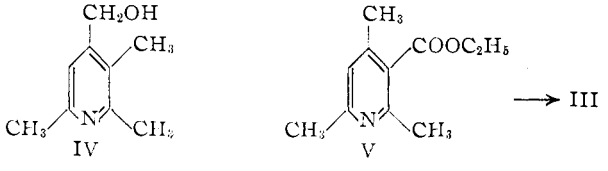
BY EDMUND C. KORNFELD

RECEIVED APRIL 7, 1955

In a previous paper[1] it was shown that reduction of diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate (I) with lithium aluminum hydride gave either the corresponding glycol (II) or a monohydric alcohol ($C_9H_{13}NO$) depending on the conditions used. The



latter product was formulated as III by analogy with the known reductive cleavage of pyridoxine to desoxypyridoxine,[2] and this alternative was favored in a review by Rudinger, Ferles and Protiva.[3] However, an unequivocal proof of structure was lacking. Subsequently Gaylord[4] suggested that the alternative formulation IV was preferred over III by analogy with the course of a number of other hydrogenolysis reactions effected by lithium aluminum hydride. In order to resolve this question we have now synthesized III by reduction of the ester V.[5]



The alcohol III so obtained, m.p. 87–88.5°, was not identical with the isomer, m.p. 127–128°, derived from I. Since the structure of III was established by its derivation from V, the monohydric alcohol obtained from I must be formulated as IV and not III. The 4-hydroxymethyl isomer IV was also obtained when the glycol II was subjected to catalytic hydrogenolysis in the presence of palladium catalyst. It is evident, therefore, that both chemical and catalytic reduction result in cleavage of the hydroxymethyl group in the 3-position, and the conclusion of Gaylord[4] appears to be correct.

(1) R. G. Jones and E. C. Kornfeld, THIS JOURNAL, **73**, 107 (1951).
(2) S. Harris, *ibid.*, **62**, 3203 (1940).
(3) J. Rudinger, M. Ferles and M. Protiva, *Chem. Listy*, **45**, 309 (1951).
(4) N. G. Gaylord, *Experientia*, **10**, 166 (1954).
(5) R. Michael, *Ann.*, **225**, 121 (1884); A. Hantzsch, *ibid.*, **215**, 42 (1882).

Experimental[6]

2,4,6-Trimethyl-3-hydroxymethylpyridine (III).—A solution of 1.6 g. of lithium aluminum hydride in 100 ml. of dry ether was stirred in an ice-bath, and to it was added dropwise during about 30 minutes a mixture of 8.0 g. of ethyl 2,4,6-trimethyl-3-pyridinecarboxylate and 100 ml. of ether. Stirring was continued for one-half hour at room temperature, after which the reaction mixture was treated cautiously with 3 ml. of water and 50 ml. of methanol. The suspension was saturated with carbon dioxide, filtered, and the solid was extracted twice with 50-ml. portions of hot methanol. The combined filtrates were evaporated to dryness, and the residue was taken up in chloroform. The chloroform solution was filtered, and the solvent was distilled. The residue was taken up in acetone, and the solution was filtered and then treated with dry hydrogen chloride. The salt which separated was filtered (2.1 g.) and recrystallized from a mixture of methanol and acetone, m.p. 168–170°.

Anal. Calcd. for $C_9H_{13}NO \cdot HCl$: C, 57.60; H, 7.52; N, 7.46; Cl, 18.89. Found: C, 58.09; H, 7.65; N, 7.62; Cl, 18.71.

The salt was dissolved in a little water, and the solution was treated with excess 50% aqueous sodium hydroxide. The oily product was extracted with chloroform; the extract was dried over magnesium sulfate, and the solvent was distilled. The hydroxymethyl compound was crystallized from acetone, m.p. 87.0–88.5°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.27; H, 8.66; N, 9.21.

The infrared spectrum in chloroform solution was different from that of the isomer IV, and the dissociation constant in water (pK'_a = 7.10) also differed from that of IV (pK'_a = 7.30).

2,3,6-Trimethyl-4-hydroxymethylpyridine (IV) **by Hydrogenolysis of 2,6-Dimethyl-3,4-di-(hydroxymethyl)-pyridine.**[1]—The glycol (1.0 g.) was hydrogenated for three hours at 50 pounds per square inch pressure in 50 ml. of glacial acetic acid using 1.0 g. of 5% palladium-on-carbon catalyst. The catalyst was filtered, and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in water, the excess sodium hydroxide was added. The product was extracted with three 20-ml. portions of chloroform, and the extracts were dried over magnesium sulfate and concentrated. The product was crystallized from acetone; yield 0.35 g. (39%), m.p. 127–128°. A mixture melting point with a sample obtained by lithium aluminum hydride reduction of the diester[1] I was not depressed.

(6) Melting points are uncorrected.

THE LILLY RESEARCH LABORATORIES
INDIANAPOLIS 6, INDIANA

Potential Anti-viral Agents. I. N,N-Dimethyl-N'-isopropyl-N'-(2-nitroisobutyl)-ethylenediamine Hydrochloride

BY FREDERICK LEONARD AND FLOYD E. ANDERSON

RECEIVED MARCH 23, 1955

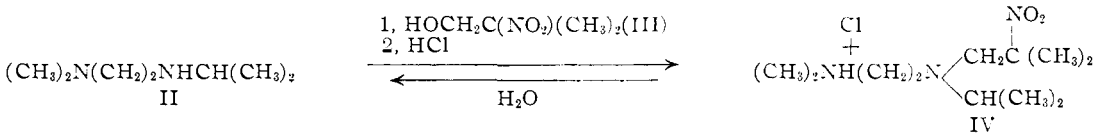
In recent years, increasing attention has been focused on the anti-viral and anti-rickettsial properties of a variety of nitro compounds. Chloram-

phenicol,[1] a group of nitro substituted acridines,[2] nitrobenzene derivatives,[3] 5-nitro-2-furfuraldehyde thiosemicarbazone[3] and a series of nitroalkane derivatives[4] are but a few examples which demonstrate that anti-viral and anti-rickettsial properties are often linked to the presence of a nitro group. It was quite reasonable therefore, when it was discovered in these laboratories that certain derivatives of dimethylaminoethylamine of the general type I, possess antiviral properties,[5] to attempt the

$$R^1R^2NCH_2CH_2N(CH_3)_2 \quad I$$

synthesis of a N,N-dimethyl-N′-alkyl-N′-nitroalkylethylenediamine for evaluation as an anti-viral agent. The synthesis and chemical properties of one such diamine, N,N-dimethyl-N′-isopropyl-N′-(2-nitroisobutyl)-ethylenediamine hydrochloride (IV) are reported in this paper.

2-Nitroalkylamines are among the most easily synthesized of nitroalkylamines since they are simply formed upon treatment of an amine with formaldehyde and a nitroparaffin or by interaction of a nitroalkanol and an amine.[6-8] Data in the literature indicate, however, that certain 2-nitroalkylamines are unstable. Lambert and Rose[9] reported that nitroamines of the general type V decompose slowly at room temperature. Senkus[10] found that steric factors largely determine the stability of 2-nitroalkylamines. Thus when R^1 and R^2 ($R^3 = R^4 = CH_3$) in V are small, the substances show marked stability, but when R^1 is isopropyl and R^2 is tetrahydrofurfuryl, 1-methylpropyl, isopropyl or even methyl, enough strain exists to make these compounds undergo reversal in water to 2-nitroisobutanol, formaldehyde and the corresponding amine. Bahner[11] claimed that salts of amines having two or three 2-nitroalkyl groups are split on heating to a nitroölefin and a lower amine. Thus VI on heating in butanol at 100° for 5 minutes yielded VII. In spite of these indications that IV might be expected to be unstable, the ease of preparation of intermediates, their anticipated facile condensation and the hope that IV might have different properties than those of compounds already described, encouraged us to undertake the preparation of IV.



II

IV

$R^1R^2NCH_2CR^3R^4$ V

$[H_3CCH_2CH(NO_2)CH_2]_2NC_4H_9 \cdot HCl$ VI

$H_3CCH_2CH(NO_2)CH_2NHC_4H_9 \cdot HCl$ VII

Condensation of 2-nitroisobutanol (III) with N,N-dimethyl-N′-isopropylethylenediamine (II) followed the general reaction scheme elaborated by Senkus[6] and Johnson[7] for the condensation of 2-nitroisobutanol (III) with primary and secondary amines, to yield N,N-dimethyl-N′-isopropyl-N′-(2-nitroisobutyl)-ethylenediamine which readily formed a hydrochloric acid addition salt IV.

N,N-Dimethyl-N′-isopropyl-N′-(2-nitroisobutyl)-ethylenediamine hydrochloride undergoes the same type of hydrolytic reversal described by Senkus[10] when heated in aqueous solution at steam-bath temperature. Workup of the reaction mixture gave an ether-soluble fraction presumably 2-nitroisobutanol or 2-nitroisobutene and an aqueous fraction from which was isolated, N,N-dimethyl-N′-isopropylethylenediamine dihydrochloride (II·2HCl) and a gummy solid which may have been very crude IV. The crystalline salt IV, on the other hand, unlike the 2-nitroalkylamines prepared by Lambert and Rose[9] showed no evidence of decomposition on storage for as long as 1.5 years.

A 0.5-mg. dose of IV, administered therapeutically (one hour post-infection), did not prevent death of embryonated eggs infected with representative viruses ranging in diameter from 16 to 600 mμ but caused a somewhat better survival of Rickettsial Pox infected eggs so treated than that observed in the case of untreated controls.

We wish to acknowledge the technical assistance of Miss Annette Stern. Dr. Fred A. Barkley kindly furnished the egg screening data.

Experimental[12]

N,N-Dimethyl-N′-isopropylethylenediamine (II).—A mixture of 208 ml. (2.5 moles) of isopropylamine, 53.8 g. (0.5 mole) of 2-dimethylaminoethyl chloride and 300 ml. of dry benzene was refluxed gently for 20 hr. cooled in an ice-bath and filtered. The filtrate was fractionated and N,N-dimethyl-N′-isopropylethylenediamine collected over the boiling range 141–142°, yield 44.9 g. (69.2%), $n^{25}D$ 1.4199. Redistillation elevated the boiling point to 142–144° and $n^{25}D$ 1.4233; picrate, m.p. 176–177° after recrystallization from ethanol.

Anal. Calcd. for $C_7H_{16}N_2 \cdot HOC_6H_2(NO_3)_3$: N, 20.1. Found: N, 19.9.

Dihydrochloride, m.p. 194–196°, after recrystallization from an ethanol–ether mixture.

Anal. Calcd. for $C_7H_{16}N_2 \cdot 2HCl$: C, 41.35; H, 9.89; N, 13.79. Found: C, 41.75; H, 9.81; N, 13.27.

N,N-Dimethyl-N′-isopropyl-N′-(2-nitroisobutyl)-ethylenediamine Hydrochloride (IV).—2-Nitroisobutanol[13] and 12 g. of N,N-dimethyl-N′-isopropylethylenediamine were mixed in a 50-ml. round-bottom flask and let stand first at room temperature for one week and then warmed at 50–60° for two days. Toluene was added to the reaction flask and

(1) J. E. Smadel and E. B. Jackson, *Science*, **106**, 418 (1947); J. E. Smadel and E. B. Jackson, *Proc. Soc. Exptl. Biol. Med.*, **67**, 478 (1948).

(2) M. D. Eaton, A. Van Allen and A. Weinar, *ibid.*, **66**, 141 (1947); J. E. Smadel, J. C. Snyder, E. B. Jackson and E. W. Hirst, *Brit. J. Pharmacol.*, **3**, 181 (1948).

(3) M. D. Eaton, C. Huang and C. G. Levenson, *Proc. Soc. Exptl. Biol. Med.*, **71**, 501 (1949).

(4) A. T. Urbanski, *Nature*, **168**, 562 (1951).

(5) Unpublished data compiled in the Dept. of Microbiology of these laboratories.

(6) M. Senkus, THIS JOURNAL, **68**, 10 (1946).

(7) H. G. Johnson, *ibid.*, **68**, 12 (1946).

(8) E. L. Hirst, J. K. N. Jones, S. Ninshan, F. W. Ochynski, A. T. Thomas and T. Urbanski, *J. Chem. Soc.*, 924 (1947).

(9) A. Lambert and J. D. Rose, *ibid.*, 1487 (1947).

(10) M. Senkus, THIS JOURNAL, **72**, 2069 (1950).

(11) C. T. Bahner, U. S. Patent 2,615,920 [*C. A.*, **47**, 5959 (1953)].

(12) Microanalyses by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y. All melting and boiling points are uncorrected.

(13) B. M. Vanderbilt and H. B. Hass, *Ind. Eng. Chem.*, **32**, 34 (1940).

the mix was distilled at water-pump pressure to remove water azeotropically. The residual oil was fractionated at 0.2 min. pressure and gave 11.6 g. of a viscous yellow oil which distilled at 103–106° and had $n^{25}D$ 1.4537. The oil was dissolved in 10 ml. of absolute ethanol and neutralized with 13.7 ml. of 3.63 *N* alcoholic hydrochloric acid while maintaining the temperature below 20°. Solvent was removed *in vacuo* (temp. 40°) leaving 13 g. of a pale-yellow wax-like solid, m.p. 108–115°, which was submitted to analysis prior to purification for identification.

Anal. Calcd. for $C_{11}H_{26}ClN_3O_2$: N, 15.7. Found: N, 15.2, 15.0.

The crude salt (10 g.) was triturated with 15 ml. of acetone, filtered and washed two times with 5-ml. portions of acetone and dried *in vacuo;* yield 7.1 g., m.p. 122–124°. After two recrystallizations (isopropyl alcohol–ether), the preparation melted with no change at 126–127°.

Anal. Calcd. for $C_{11}H_{26}ClN_3O_4$: C, 49.92; H, 9.30; N, 15.02. Found: C, 49.62; H, 9.81; N, 15.84.

Hydrolysis of N,N-Dimethyl-N'-isopropyl-N'-(2-nitroisobutyl)-ethylenediamine Hydrochloride.—A solution of 1 g. of N,N-dimethyl-N'-isopropyl-N'-(2-nitroisobutyl)-ethylenediamine hydrochloride in 5 ml. of water was heated on the steam-bath for three hours, cooled and extracted with ether. The aqueous layer was concentrated *in vacuo* leaving a gummy residue which weighed 0.45 g. Trituration of this residue with acetone gave a crystalline solid identified by melting point (195–197°) and analysis as N,N-dimethyl-N'-isopropylethylenediamine dihydrochloride (II·2HCl).

Anal. Calcd. for $C_7H_{18}N_2 \cdot 2HCl$: C, 41.35; H, 9.89. Found: C, 41.94; H, 9.57.

The acetone filtrate from IIa was evaporated leaving a gummy residue (0.08 g.) which could not be purified for identification. Evaporation of the ether extract of the reaction mixture gave an oily residue, probably 2-nitroisobutanol or 2-nitroisobutene.

RESEARCH LABORATORIES
NEPERA CHEMICAL CO., INC.
YONKERS 2, N. Y.

Chemistry of Hexachlorocyclopentadiene. V.[1] The Diels–Alder Reactions with Allylic and Halogen-containing Dienophiles

BY E. T. MCBEE, H. RAKOFF[2a] AND R. K. MEYERS[2b]

RECEIVED FEBRUARY 23, 1955

Chloroprene and its homologs can be condensed with maleic anhydride or naphthoquinone at 100°; 1-chlorobutadiene and 2,3-dichlorobutadiene do not react under these conditions.[3] Although cyclopentadiene is more reactive than open-chain dienes, it was not predictable that hexachlorocyclopentadiene would undergo the Diels–Alder reaction at 100° with dienophiles such as maleic anhydride, *p*-benzoquinone, acrylonitrile and methyl vinyl ketone[4] or cyclopentadiene.[5,6] Similarly the fact that hexachlorocyclopentadiene would condense with allylic dienophiles and halogenated olefins which enter into the Diels–Alder reaction with the usual dienes only at elevated temperatures was unpredictable.

The adduct of hexachlorocyclopentadiene and allyl alcohol was prepared by refluxing the components with xylene. This adduct was converted to the acetate and propionate esters.

Certain halogen-containing olefins were found to undergo the diene synthesis with hexachlorocyclopentadiene at 200°. Of eighteen olefins investigated, only the following gave adducts: 1,2-dichloroethylene, 1,2-dibromoethylene, 1-chloropropene and 1,3-dichloropropene. Tetrachloroethylene, 1,1-dichloropropene, 1,2-dichloropropene, 1,1,2-trichloropropene, 1,2,3,3-tetrachloropropene, 1,1,2,3,3-pentachloropropene, 1,1,2-trichloro-3,3,3-trifluoropropene, 1,1,2,3-tetrachloro-3,3-difluoropropene and 2,3-dichlorohexafluoro-2-butene were unreactive at 200°. Vinylidene dichloride, tetrafluoroethylene, *asym*-dichlorodifluoroethylene and 2,3-dichloropropene underwent only dimerization or polymerization reactions. A comparison of the halogenated olefins indicates that two chlorine atoms on one double-bonded carbon inhibit the Diels–Alder reaction. Similarly, olefins with the structure $-\overset{|}{C}=CCl-R$ do not react. It is concluded that a halogenated dienophile to undergo reaction with hexachlorocyclopentadiene under the described conditions must have at least one hydrogen atom on each of the double bonded carbons.

Experimental[7]

1,2,3,4,7,7-Hexachloro-5-hydroxymethylbicyclo[2.2.1]-2-heptene.—A mixture of allyl alcohol (65 g., 1.1 moles) and hexachlorocyclopentadiene (273 g., 1 mole) in 25 ml. of xylene was refluxed for 2 days. Low-boiling materials were removed by distillation, and the residual red-brown solid was decolorized and crystallized from ligroin (b.p. 90–100°). Two recrystallizations from the same solvent gave 178 g. (53%) of the colorless adduct, m.p. 162–165°. An additional crystallization raised the melting point to 164–165°.[8]

Anal. Calcd. for $C_8H_6Cl_6O$: Cl, 64.3. Found: Cl, 64.1.

Acetate.—The adduct (16 g.), when refluxed for 18 hours with acetic anhydride (8 g.) in benzene (25 ml.) yielded 14.5 g. (81%) of ester boiling at 144–146° (1 mm.). The analytical sample was fractionated from a small column and boiled at 154–155° (2 mm.), $n^{20}D$ 1.5332.

Anal. Calcd. for $C_{10}H_8Cl_6O_2$: C, 32.2; H, 2.14. Found: 32.2; H, 2.06.

Propionate.—The same procedure furnished 87% of propionate ester, b.p. 160–161° (2 mm.), $n^{20}D$ 1.5322.

Anal. Calcd. for $C_{11}H_{10}Cl_6O_2$: C, 34.1; H, 2.58. Found: C, 34.3; H, 2.56.

1,2,3,4,7,7-Hexachloro-5-chloromethylbicyclo[2.2.1]-2-heptene.—Allyl chloride (20 g., 0.26 mole) and hexachlorocyclopentadiene (70 g., 0.26 mole) were sealed in a Carius tube and heated to 125° for 18 hours. The tube was cooled and opened and the contents were distilled under reduced pressure to give 61 g. (68%) of adduct, b.p. 130–131° (3 mm.), which crystallized on standing to give a solid, m.p. 54–55°.[8]

Anal. Calcd. for $C_8H_5Cl_7$: Cl, 71.1. Found: Cl, 70.5.

1,2,3,4,7,7-Hexachloro-5-bromomethylbicyclo(2.2.1)-2-heptene was prepared in an analogous fashion to the chloride but at lower temperature (85–95°), m.p. 79–80°, in agreement with Fields.[6]

(1) For paper IV, see E. T. McBee, H. E. Ungnade, H. Rakoff and K. Dinbergs, THIS JOURNAL, **77**, 4379 (1955).

(2) (a) A portion of a thesis by H. Rakoff submitted to Purdue University in partial fulfillment of the requirments for the degree of Doctor of Philosophy, 1950. (b) A portion of a thesis by R. K. Meyers submitted to Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1950.

(3) D. D. Coffman and W. H. Carothers, THIS JOURNAL, **55**, 2040 (1933).

(4) E. A. Prill, *ibid.*, **69**, 62 (1947).

(5) Velsicol Corporation, British Patent 614,931 (Dec. 30, 1948); S. H. Herzfeld, R. E. Lidov and H. Bluestone, to Velsicol Corporation, U. S. Patent 2,606,910 (Aug. 12, 1952).

(6) Subsequent to the completion of this work in 1950, the adducts of hexachlorocyclopentadiene with allyl alcohol, allyl chloride and allyl bromide have been described by E. K. Fields, THIS JOURNAL, **76**, 2709 (1954), and with vinyl chloride by H. Bluestone, U. S. Patent 2,670,132, April 20, 1954.

(7) All melting points are uncorrected. Analyses were done at Purdue University.

(8) Fields[6] reported a 43% yield b.p. 142–144° (3.7 mm.), but the isolation of no solid.